

EDITORIAL COMMENT

Phosphodiesterase-4 Activity

A Critical Modulator of Atrial Contractility and Arrhythmogenesis*

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Atrial excitation-contraction coupling (ECC) and pacemaker activity are both dependent on intracellular calcium (Ca^{2+}) cycling, and alterations in Ca^{2+} cycling are strongly implicated in the pathophysiology of atrial fibrillation (AF). Depolarization of cardiac myocytes promotes Ca^{2+} influx via L-type calcium channels (LTCCs), which then releases a larger quantity of Ca^{2+} from intracellular stores. For ECC, elevated Ca^{2+} interacts with troponin C, promoting cross bridge interaction and myocyte contraction. Relaxation during diastole requires intracellular Ca^{2+} levels to return to baseline levels, either via reuptake of Ca^{2+} into the sarcoplasmic reticulum or extrusion from the cell by the sodium calcium exchanger. In pacemaking cells, Ca^{2+} influx via the LTCC underlies the upstroke of the action potential; Ca^{2+} (and sodium) influx via HCN (hyperpolarization-activated cyclic nucleotide-gated) channels regulates the rate of diastolic depolarization.

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Given the critical role of Ca^{2+} cycling in atrial contractile and pacemaker functions, it is not surprising that these processes are highly regulated. Sympathetic nerve activity increases heart rate and cardiac output by increasing Ca^{2+} influx and cycling in both the sinoatrial (SA) node and in the working atrial myocardium. Norepinephrine released from cardiac nerve terminals activates beta-adrenergic receptors (beta-ARs) in the heart. Beta-AR activation increases production of cyclic adenosine monophosphate

(cAMP). Parasympathetic (vagal) activity suppresses formation of cAMP, by inhibiting the activity of adenylate cyclase. Elevated cAMP levels increase protein kinase A (PKA) activity, promoting the phosphorylation of the LTCC, ryanodine receptor, HCN channels, troponin I, and phospholamban. Thus, during sympathetic stimulation, Ca^{2+} influx is enhanced, heart rate is increased, the Ca^{2+} transient is larger, contractile activity is increased, and reuptake of Ca^{2+} into the sarcoplasmic reticulum is enhanced. Enhanced Ca^{2+} cycling comes at the cost of increased demand for adenosine triphosphate, oxygen, and metabolic substrates.

When sympathetic activation subsides, intracellular phosphodiesterases (PDEs) degrade cAMP, reducing PKA activity. Atrial PDEs are important modulators of heart rate, cardiac contractility, and energy demand. Too little PDE activity can lead to prolonged tachycardia, increased contractile activity, and enhanced pacemaker activity—both in the sinoatrial node and in secondary pacemakers (such as those in the pulmonary vein region or around the mitral valve). This can promote Ca^{2+} overload, initiate myocyte apoptosis, and act as a trigger for AF. Too much PDE activity can diminish the ability of the heart to respond to stress and reduce cardiac contractile activity. We and others have shown that in persistent AF, perhaps as an adaptation to rate-induced intracellular Ca^{2+} overload, Ca^{2+} influx through the LTCC is reduced (1), leading to impaired contractility, and increasing risk of thrombus formation and stroke (2). PDEs thus have a significant impact on atrial contractile and electrical activity, and can affect risk of AF and stroke.

PDE isoforms vary in substrate specificity (degrading cAMP, cyclic guanosine monophosphate, or both). They have different kinetics and affinity for cyclic nucleotides. The intracellular localization and regional distribution of PDEs vary. PDE3 is the most abundant PDE expressed in human atria. Previous pharmacological studies characterized, in detail, the impact of PDE3 inhibitors on the adrenergic responses of human atrial myocyte contractility and calcium currents (3–5). Although PDE3 is the most abundant PDE in the human atrium, it is not the only isoform.

In this issue of the *Journal*, Molina et al. (6) carefully document the presence, function, and significance of PDE4 (A, B, and D) isoforms in human atrial myocytes. Using a combination of classical and state-of-the-art techniques, the investigators synthesize a novel and coherent understanding of the physiological significance of PDE4 in human atria. The authors show that although PDE4 constitutes only about 15% of total PDE activity, PDE4 isoforms have a very significant impact on cAMP levels and on the Ca^{2+} channel response to beta-ARs agonists. They demonstrate that PDE4 A, B, and D isoforms are expressed in human atrial myocytes, and report that PDE4D is the most abundant. In isolated human atrial myocytes, pharmacological inhibition

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of PDE4 activity during exposure to beta-ARs was associated with a prolongation of the increase in cAMP levels. PDE4 inhibition increased LTCC density and increased the rate of spontaneous sarcoplasmic reticulum calcium release events. Similarly, in intact human atrial trabeculae, inhibition of PDE4 activity increased the contractile response to beta-ARs and increased arrhythmic contractile activity.

Interestingly, the investigators were able to assess PDE activity in right atrial tissues from 18 patients in sinus rhythm and 7 patients with permanent AF. Total PDE activity was ~25% lower in patients with AF compared with those in sinus rhythm ($p = 0.059$). The difference was even greater with respect to PDE4 activity, which was reduced by 48% in AF patients versus those in sinus rhythm ($p = 0.029$). The investigators noted (not surprisingly) that the AF patients were older than those in sinus rhythm. Regression analysis confirmed that PDE4 activity was negatively associated with age. In an age-matched comparison, the difference between patients with AF versus those in sinus rhythm was smaller, but still approached statistical significance ($p = 0.057$). It thus seems likely that loss of PDE4 activity contributes to AF risk, and that the presence of AF is associated with a further reduction in PDE4 activity. Although a number of pro-arrhythmic pathways (sympathetic tone, hypertension, fibrosis, and so on.) also increase in prevalence with age, the results of Molina et al. (6) are intriguing.

These studies suggest that, by minimizing Ca^{2+} influx and spontaneous release events, PDE4 decreases the frequency of Ca^{2+} release mediated ectopic events and protects against arrhythmic activity. The studies in this report focused on right atrial appendage tissue specimens. As much of the current clinical focus on AF treatment centers on isolation of ectopic activity originating in the pulmonary vein region of the left atrium, it would be of interest in future studies to evaluate the regional abundance and distribution of PDE isoforms in the left and right atrial bodies, appendages, SA and atrioventricular nodes, and in the pulmonary vein region.

A primary concern for AF patients is the risk of cardioembolic stroke; AF increases risk of stroke 5- to 7-fold (7). Molina et al. (6) note that PDE4D has been linked to stroke risk in genome-wide association studies with stroke endpoints (8,9), but point out that these studies have not yet considered the possibility that atrial PDE4D may underlie this relationship. On the basis of the results presented, this seems to be a logical and important hypothesis. In genome wide association studies of AF cohorts (10,11), it will be possible to assess the role of PDE4D as a candidate gene associated with stroke risk. In such a study, if the number of strokes reported is sufficient, it should be straightforward to

evaluate the hypothesis that atrial PDE4D activity is causally related with stroke as a result of AF.

AF is the most common arrhythmia, and currently available antiarrhythmic treatments based on ion channel blockade have limited efficacy. Considerable recent effort has focused on the development of novel anticoagulants that help to reduce stroke risk in AF. Although these agents are welcomed and are likely to be exceptionally valuable, the study of Molina et al. (6) suggests the intriguing hypothesis that novel agents that selectively enhance PDE4D activity might simultaneously prevent atrial contractile dysfunction, limit atrial energy demands associated with Ca^{2+} cycling, help to prevent AF, and decrease stroke risk. Efforts to test this hypothesis would represent a significant step toward more effective management of AF.

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